The Nobel Prize in Chemistry 2013 for the Development of Multiscale Models of Complex Chemical Systems: A Tribute to Martin Karplus, Michael Levitt and Arieh Warshel

This year, the Royal Swedish Academy of Sciences is honoring the pioneers of molecular dynamics simulations, Martin Karplus, Michael Levitt and Arieh Warshel, for the "development of multiscale models of complex chemical systems". The necessity to predict and understand biological processes and complex chemical reactions was one of the great challenges in the 1970s. While classical Newtonian physics was limited to analyzing molecules at a state of rest, quantum physics was able to simulate the excited states of molecules in chemical reactions. However, the limitation of the latter was the absence of powerful computers capable of integrating the vast amount of data any larger protein would require. The accomplishment of the three laureates was to successfully design a computer program that combined classical and quantum physics principles, allowing calculation of every possible reaction pathway using computer simulation, in other words, a program capable of modeling any molecule, even very large biological molecules such as enzymes (Fig. 1) [1].

Martin Karplus, Michael Levitt and Arieh Warshel published in the *Journal of Molecular Biology* numerous major studies on protein folding and packing, prediction of macromolecular structures, protein–ligand interactions, protein energetics and theories of enzymatic mechanisms [1–12]. Martin Karplus worked on the characterization of the relationship between inherent flexibility of proteins and their propensity to conformational changes [2,13]. His Karplus equation and its derived forms still serve as a reference for protein structure resolution from NMR spectra [14]. Michael Levitt served as a member on editorial board of the *Journal of Molecular Biology* for the past decade and has made significant contributions to the field of protein folding by establishing algorithms allowing the first identification of protein secondary structure based on atomic coordinates, deciphering close range interactions in secondary structure elements or showing that lower energy side-chain conformations are favored during folding [15–17]. He is equally known for his approaches to refine protein coordinates in X-ray structures [18]. Arieh Warshel's work on molecular simulations is considerable. In addition to the quantum mechanical/molecular mechanics method [1], he developed the empirical valence bond and quantum mechanical(valence bond)/molecular mechanics methods for simulation of enzymatic reactions in solution [19,20] and enhanced the protein-dipoles Langevin-dipoles model for calculation of electrostatic energies in proteins [21]. The collective work of Martin Karplus, Michael Levitt and Arieh Warshel paved the way to modern chemistry by providing many essential theoretical tools that significantly benefit the experimental approaches and our overall understanding of complex chemical systems.

The *Journal of Molecular Biology* congratulates the three laureates for their Nobel Prize and salutes their lasting contribution to the fields of chemistry, molecular biology and biophysics. You may openly access most of these papers via the Elsevier Nobel tribute page http://www.elsevier.com/about/history/nobel-tribute/2013-nobel-prize-laureates/2013-nobel-prize-in-chemistry/articles.

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Theoretical Studies of Enzymic Reactions:

Dielectric, Electrostatic and Steric Stabilization of the Carbonium Ion in the Reaction of Lysozyme

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A general method for detailed study of enzymic reactions is presented. The method considers the complete enzyme-substrate complex together with the surrounding solvent and evaluates all the different quantum mechanical and classical energy factors that can affect the reaction pathway. These factors include the quantum mechanical energies associated with bond cleavage and charge redistribution of the substrate and the classical energies of steric and electrostatic interactions between the substrate and the enzyme. The electrostatic polarization of the enzyme atoms and the orientation of the dipoles of the surrounding water molecules is simulated by a microscopic dielectric model. The solvation energy resulting from this polarization is considerable and must be included in any realistic calculation of chemical reactions involving anything more than an isolated molecule in *vacuo*. Without it, acidic groups can never become ionized and the charge distribution on the substrate will not be reasonable. The same dielectric model can also be used to study the reaction of the substrate in solution. In this way the reaction in solution can be compared with the enzymic reaction.

In this paper we study the stability of the carbonium ion intermediate formed in the cleavage of a glycosidic bond by lysozyme. It is found that electrostatic stabilization is an important factor in increasing the rate of the reaction step that leads to the formation of the carbonium ion intermediate. Steric factors, such as the strain of the substrate on binding to lysozyme, do not seem to contribute significantly.

Fig. 1. "Theoretical studies of enzymic reactions: dielectric, electrostatic and steric stabilization of the carbonium ion in the reaction of lysozyme" published in Journal of Molecular Biology in 1976.

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